

Effect of hyaluronidase on mortality and morbidity in patients with early peaking of plasma creatine kinase MB and non-transmural ischaemia

*Multicentre investigation for the limitation of infarct size (MILIS)**

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SUMMARY A multicentred, randomised, blind study was started in 1978 to compare propranolol or hyaluronidase with placebo in patients with acute myocardial infarction admitted within 18 hours of onset of symptoms. Patients were randomised to group A and received hyaluronidase, propranolol, or placebo, or, if propranolol was contraindicated, to group B and received hyaluronidase or placebo. Hyaluronidase (500 U/kg given every six hours for 48 hours) had no effect on mortality or infarct size in the overall population. Because spontaneous reperfusion was more common in patients with early peaking of plasma creatine kinase MB or non-transmural electrocardiographic changes or both, the results were reanalysed for two subgroups: those in whom plasma creatine kinase peaked < 15 hours after the onset of symptoms (early peak, n = 184) and those with a peak > 15 h after the onset of symptoms (late peak, n = 546). The distribution of time to peak activity of creatine kinase MB was similar in the hyaluronidase and placebo groups. In the early peak patients who were given hyaluronidase (groups A and B) total mortality and cardiac-specific four year mortality were significantly lower. This was most pronounced in group B in which the total mortality was 45% and cardiovascular mortality was 47% less than in the placebo group. Similarly, mortality from cardiovascular disease in patients (groups A and B) with non-transmural ischaemia (ST-T changes) given hyaluronidase was significantly lower, with group B showing a 50% reduction. In the subsets of patients with late peaking of creatine kinase MB or those presenting with transmural electrocardiographic changes there was no difference in total mortality or deaths from cardiac disease between those given hyaluronidase and those given placebo.

Hyaluronidase was associated with improved survival in patients with early peaking of plasma creatine kinase MB, suggesting the possibility of salvage of myocardium in patients who have early spontaneous reperfusion and possibly after therapeutic reperfusion.

The results of treatment with hyaluronidase in the Multicenter Investigation for the Limitation of

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Infarct Size (MILIS) were recently reported.¹ The trial included 431 patients randomised to placebo and 420 to hyaluronidase. Infarct size, the primary end point, and survival were not significantly different in those on placebo or hyaluronidase in the total population studied. None the less, a trend that favoured survival in the hyaluronidase group was noted in a prospectively defined subgroup of patients in whom propranolol was contraindicated (group B).

Left ventricular ejection fraction, a secondary end point in patients randomised to group B, increased more between entry (pretreatment) and 8–10 days later in patients treated with hyaluronidase than in the placebo group; this difference was only of borderline significance ($p < 0.06$).

To identify possible beneficial effects of hyaluronidase in subgroups of patients, additional analyses were performed retrospectively and these analyses form the basis of the present report. Although we recognise that such retrospective subgroup analyses must be interpreted with caution and cannot provide definitive results, they can provide useful insights and hypotheses for future testing.

Patients and methods

The overall design of the trial has been presented in detail^{1–3}; only aspects pertinent to the subgroup analyses are presented here.

PROSPECTIVE SUBGROUPS

The patients enrolled in MILIS were suspected of having acute myocardial infarction on the basis of chest pain and electrocardiographic changes. Analysis of the plasma activity of creatine kinase MB confirmed myocardial infarction in 87% of randomised patients.² Patients were stratified prospectively into either group A (propranolol acceptable) or group B (propranolol contraindicated). The major reasons patients were entered into group B were moist rales involving a third or more of the lung fields (44%), ventricular rate of 55 beats/minute or less at randomisation or an episode of less than 40 beats/minute before anticholinergic treatment (30%), systolic arterial pressure of less than 100 mm Hg, a decrease of 50 mm Hg (23%), pulmonary oedema (19%), and asthma (15%). Group A patients were randomised to placebo, propranolol, or hyaluronidase, and group B patients to either placebo or hyaluronidase. Patients were only admitted to the trial within 18 hours from the onset of symptoms.

RETROSPECTIVELY IDENTIFIED SUBGROUPS

Since the start of the trial in August 1978, substantial information has accrued which indicates that Q wave myocardial infarction is frequently caused by thrombotic coronary occlusion.⁴⁵ There is also evidence to suggest that in some patients there is early spontaneous reperfusion⁶⁷ which is more likely to be associated with early peaking of plasma creatine kinase MB and with only ST-T wave changes rather than Q waves.⁸⁹ Presumably the early peaking reflects more rapid washout of the enzyme, which

also occurs when pharmacological thrombolysis^{10–12} and mechanical intervention produce reperfusion.^{13 14} Non-Q-wave infarction is also associated with early peaking of plasma creatine kinase MB activity (a mean of 15 hours after onset of symptoms compared with patients with Q wave infarction in whom this peak occurs on average 17 hours after the onset of symptoms).¹⁵ The results of early cardiac catheterisation show that Q wave infarction is associated with complete occlusion of the infarct related vessel. In contrast, non-Q-wave infarction is more likely to be caused by incomplete infarction,¹⁶ suggesting that non-Q-wave infarction is associated with early reperfusion leaving extensive residual, viable but jeopardised myocardium.¹⁷ The most recent implications for this hypothesis come from coronary angiography and thallium perfusion studies.¹⁷ Extensive ischaemia (detected by thallium scintigraphy after exercise) and clinical events such as reinfarction and death were more common after non-Q-wave infarction than after Q wave infarction.

Retrospective analyses were performed to determine whether hyaluronidase had a different effect in patients suspected of undergoing spontaneous reperfusion because they had early peaking of plasma creatine kinase MB activity or non-Q-wave changes on the pretreatment electrocardiogram. We compared the effects of hyaluronidase and placebo on two end points: (a) mortality (both total and cardiovascular) and (b) the change in the left ventricular ejection fraction from the pretreatment value to that obtained 8–10 days after treatment. In the groups defined by the time to peak plasma creatine kinase MB we assessed only patients with confirmed myocardial infarction. In the group defined by the pretreatment electrocardiogram, patients were included if they satisfied the inclusion criteria, whether or not serial concentrations of plasma creatine kinase MB showed them to have sustained an acute myocardial infarction.

“Early peaking” of plasma creatine kinase MB activity was defined as occurring within 15 hours after onset of symptoms and “late peaking” as occurring more than 15 hours after onset. Fifteen hours represents the 25th percentile of the distribution of time from onset of symptoms to peak creatine kinase MB for MILIS patients with an abnormal increase in creatine kinase MB. We chose 15 hours because of the following observations in patients undergoing reperfusion. (a) Pharmacologically induced early thrombolysis leads to peaking of plasma creatine kinase MB around 12–16 hours after the onset of symptoms. (b) In patients with non-transmural infarction plasma creatine kinase MB peaks on average 15 hours after the onset of symptoms.¹⁵ (c) Patients in whom spontaneous reperfusion

is suspected reach peak plasma creatine kinase MB activity from 12 to 26 hours after the onset of symptoms,¹⁶ which is similar to the time at which creatine kinase MB peaks after pharmacologically induced reperfusion.^{11,12} Although there are limitations to the degree of correlation between the electrocardiogram and the anatomical extent of the infarct^{18,19} in this study, "non-transmural ischaemic changes" are taken to refer to ST segment depression without new Q waves. "Transmural ischaemic changes" refer to ST segment elevation or abnormal new Q waves or both. Sixty nine patients in whom electrocardiographic classification into non-transmural or transmural ischaemia was not possible were excluded from analysis (for example, patients with conduction defects on the pretreatment electrocardiogram).

Patients were followed up three and six months after discharge. Subsequently, semi-annual reports on the health of the patient were completed either by personal or telephone interview. Long-term follow up was obtained from all but two of the 851 patients. Follow up efforts were extended six months after recruitment ceased to attain a minimum of six months of follow up on all randomised patients. Survival curves and mortality rates are based on a cut off of four years of follow up experience.

STATISTICAL ANALYSIS

We used *t* tests for quantitative data, χ^2 tests for qualitative data for baseline comparisons between treatments, actuarial life table techniques²⁰ and Cox proportional hazards methods²¹ for the mortality analysis, and analyses of covariance for the comparisons of change in ejection fraction with different treatments. The generalised Savage (Mantel-Cox) statistic is reported in the unadjusted mortality analysis. The Cox proportional hazards analysis incorporated, as a covariate, a linear risk score¹ developed from baseline variables predictive of mortality in which there was some indication of imbalance between treatments. If the baseline ejection fraction used in the risk score was missing we used the mean ejection fraction among patients in whom the measurement was made. The covariance analysis of the change in the ejection fraction included the initial ejection fraction as an adjustment covariable.

Results

BASELINE CHARACTERISTICS

A total of 851 patients was analysed: 338 were in group A (172 randomised to placebo and 166 to hyaluronidase) and 513 were in group B (259 randomised to placebo and 254 to hyaluronidase). The

baseline characteristics (27 variables) were compared among patients who received either placebo or hyaluronidase in the entire patient group (*n* = 851), in those in group B (*n* = 513), in those with early peaking of creatine kinase MB curves (*n* = 184), and in patients showing non-transmural ischaemia (*n* = 146). There were few significant differences between patients treated with placebo and hyaluronidase in the entire patient group or in any of the subgroups, indicating good balance between the placebo treated and hyaluronidase treated groups.

INFARCT SIZE INDEX

Data for the calculation of the infarct size index were adequate in 133 patients treated with placebo or hyaluronidase with early peaking of plasma creatine kinase MB activity and 491 with late peaking. Mean (SD) infarct size index in the group with early peaking was 12.6 (1.2) creatine kinase g eq/m², which was a mean of 67% of that in the late peaking group (18.9 (0.6), *p* < 0.0001). There was no significant difference in infarct size index assessed by plasma creatine kinase MB between the placebo treated and hyaluronidase treated groups for the total population or for prospectively identified subgroups.¹

MORTALITY

A comparison of early and late peaking of plasma creatine kinase MB

There was no significant difference between the overall survival of the placebo treated and hyaluronidase treated patients over the four year follow up

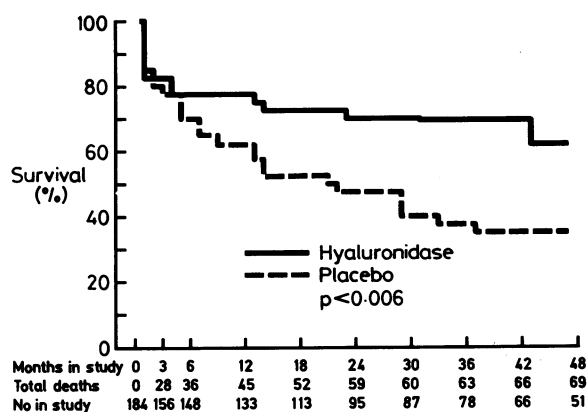


Fig 1 Comparison of the survival curves over a four year period for patients treated with hyaluronidase or placebo who showed early peaking of plasma activity of creatine kinase MB (≤ 15 hours from onset of symptoms) in groups A and B combined. There was a statistically significant improvement in the survival of patients treated with hyaluronidase (*p* < 0.006).

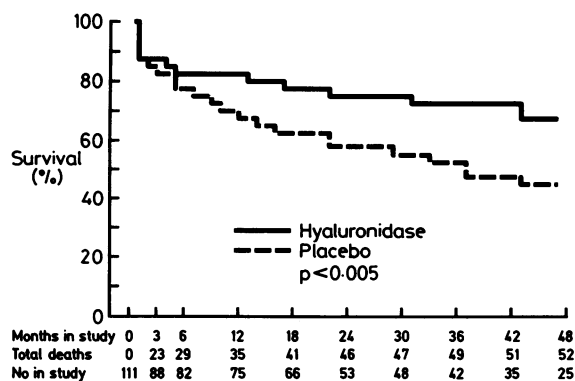


Fig 2 Comparison of the survival curves over a four year period for patients treated with hyaluronidase or placebo who showed early peaking of plasma creatine kinase MB activity (≤ 15 hours from onset of symptoms) enrolled in group B. There was a statistically significant improvement in the survival of patients treated with hyaluronidase ($p < 0.005$).

interval.¹ None the less, a trend in favour of hyaluronidase was noted in group B (a mortality of 37% in placebo treated patients and 31% in hyaluronidase treated patients), but this difference did not achieve statistical significance. Similar results were obtained when the end point was restricted to deaths related to cardiovascular disease. Among all patients with early peaking of plasma creatine kinase MB (groups A and B), hyaluronidase treated patients had a four year mortality of 29% compared with 47% in the placebo group ($p < 0.006$ unadjusted and 0.05 if adjusted for baseline differences (fig 1). The lower mortality in hyaluronidase treated patients with early peaking of plasma creatine kinase MB was most apparent in patients in group B in whom the four year mortality was 0.34, compared with the placebo group in which it was 0.62 (fig 2) ($p < 0.08$ adjusted and

0.005 unadjusted). Similar results were obtained when the end point was death from cardiovascular disease (table 1). Unlike patients with early peaking of plasma creatine kinase MB, in those who had late peaking of plasma creatine kinase MB there was no difference in total mortality or cardiovascular mortality between patients treated with placebo or hyaluronidase in group A or group B, or in groups A and B combined.

In patients in group B who showed non-transmural electrocardiographic changes, both total mortality and deaths from cardiovascular disease were significantly lower in patients treated with hyaluronidase (table 3, fig 3). There were no differences in either the total or cardiovascular-related mortality between placebo and hyaluronidase treated patients in the group that showed transmural electrocardiographic changes on admission in either the overall group or in any of the subgroups.

In summary, comparison of the survival data between the placebo treated and hyaluronidase treated patients showed a beneficial effect in the hyaluronidase treated patients who showed early peaking of plasma creatine kinase MB and in patients who showed electrocardiographic findings that were characteristic of non-transmural ischaemia before treatment. This effect produced a lower frequency of both total deaths and those caused by cardiovascular disease in these subgroups of patients receiving hyaluronidase, and was present in the total patient population and in patients in group B.

EJECTION FRACTION

Prospective analyses

As indicated in the previous report,¹ for the total patient population the mean change in left ventricular ejection fraction measured by radionuclide

Table 1 Comparison of cardiovascular mortality on different treatments by patient group and by time from onset to peak creatine kinase MB

Group	Time to peak	Treatment	No	Crude death rate (%)	p value	
					Unadjusted	Adjusted
A and B	≤ 15 h	Placebo	87	43	0.01 (H)*	0.07 (H)
		Hyaluronidase	97	26		
	> 15 h	Placebo	288	22	0.65	0.13
		Hyaluronidase	258	19		
A	≤ 15 h	Placebo	35	20	0.68	0.57
		Hyaluronidase	38	18		
	> 15 h	Placebo	115	12	0.75	0.61
		Hyaluronidase	98	10		
B	≤ 15 h	Placebo	52	58	0.006 (H)	0.08 (H)
		Hyaluronidase	59	31		
	> 15 h	Placebo	173	28	0.63	0.14
		Hyaluronidase	160	25		

*Indicates the treatment with the lower mortality: H, hyaluronidase.

Table 2 Comparison of cardiovascular mortality on different treatments by patient group and pretreatment electrocardiographic findings

Group	Type	Treatment	No	Crude death rate (%)	p value	
					Unadjusted	Adjusted
A and B	Non-transmural	Placebo	74	38	0.04 (H)*	0.03 (H)
		Hyaluronidase	72	24		
	Transmural	Placebo	327	22	0.51	0.23
		Hyaluronidase	309	20		
A	Non-transmural	Placebo	26	15	0.51	0.46
		Hyaluronidase	30	23		
	Transmural	Placebo	140	14	0.61	0.37
		Hyaluronidase	122	11		
B	Non-transmural	Placebo	48	50	0.007 (H)	0.006 (H)
		Hyaluronidase	42	24		
	Transmural	Placebo	187	28	0.53	0.43
		Hyaluronidase	187	25		

*Indicates the treatment with the lower mortality: H, hyaluronidase.

ventriculography between pretreatment and 8–10 days after treatment was similar in the groups treated with placebo and hyaluronidase. In group B, however, the mean (SE) improvement in ejection fraction in patients treated with hyaluronidase (3.1 (1.0)) was significantly greater than in patients treated with placebo (0.5 (0.9), $p = 0.06$).

RETROSPECTIVE ANALYSES

Comparison of groups with early and late peaking of creatine kinase MB

There were no significant differences between patients treated with placebo and patients treated with hyaluronidase in the change in ejection fraction over the 8–10 days treatment for the group with late peaking of plasma creatine kinase MB. In patients in group B with early peaking of creatine kinase MB, however, there was greater improvement in patients receiving hyaluronidase (by 7.8 (2.1) units) than in

the placebo group (3.2 (2.0) units) ($p = 0.06$) (table 3).

In patients with “non-transmural” electrocardiographic changes in group B, the ejection fraction rose more (9.7 (2.7) units) on hyaluronidase than on placebo (1.9 (2.1) units) ($p < 0.007$) (table 4). Treatment with hyaluronidase in patients with “transmural” electrocardiographic changes did not improve ejection fraction either in groups A or B or in groups A and B together. Thus patients with a significant improvement in ejection fraction were found only in group B and were characterised by electrocardiographic findings of non-transmural ischaemia. In patients in group B who had early peaking of plasma creatine kinase MB activity there was also a tendency for hyaluronidase to improve ejection fraction.

Patients with “non-transmural” electrocardiographic changes were evenly distributed between

Table 3 Comparison of the change in ejection fraction on different treatments by patient group and time from onset to peak creatine kinase MB plasma concentration

Group	Time to peak	Treatment	No	Ejection fraction			p value
				Pretreatment	10 days	Change	
A and B	≤ 15 h	Placebo	54	41.4 (1.9)	45.9 (2.6)	4.5 (1.6)	0.51
		Hyaluronidase	66	45.4 (2.0)	50.8 (2.0)	5.3 (1.6)	
	> 15 h	Placebo	201	47.7 (1.1)	47.5 (1.0)	-0.1 (0.7)	0.26
		Hyaluronidase	188	47.0 (1.1)	48.1 (1.0)	1.2 (0.8)	
A	≤ 15 h	Placebo	23	44.3 (3.1)	50.5 (4.4)	6.3 (2.6)	0.25
		Hyaluronidase	27	48.6 (3.4)	50.4 (3.6)	1.8 (2.4)	
	> 15 h	Placebo	88	49.3 (1.5)	49.9 (1.5)	0.5 (1.2)	0.65
		Hyaluronidase	75	51.3 (1.7)	52.0 (1.7)	0.7 (1.1)	
B	≤ 15 h	Placebo	31	39.3 (2.4)	42.5 (3.0)	3.2 (2.0)	0.06 (H)*
		Hyaluronidase	39	43.2 (2.4)	51.0 (2.4)	7.8 (2.1)	
	> 15 h	Placebo	113	46.4 (1.5)	45.7 (1.4)	-0.7 (1.0)	0.27
		Hyaluronidase	113	44.1 (1.4)	45.6 (1.3)	1.5 (1.1)	

*Indicates the treatment associated with the greatest improvement in ventricular function: H, hyaluronidase. Values shown are mean (SEM).

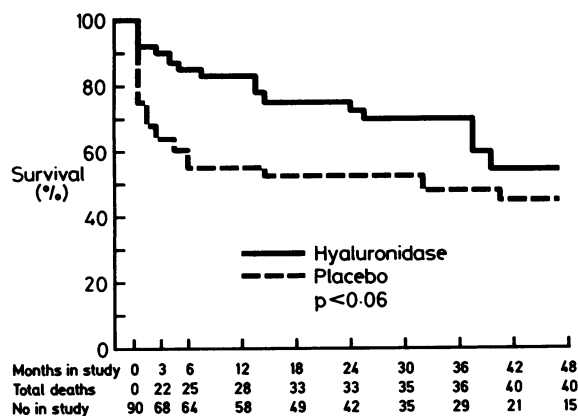


Fig 3 Comparison of the survival curves over a four year period for patients treated with hyaluronidase or placebo who showed non-transmural changes on the pretreatment electrocardiogram and were enrolled in group B. There was an improvement in the survival of patients treated with hyaluronidase ($p < 0.06$).

placebo and hyaluronidase groups. None the less, there was a significant association between the type of electrocardiographic change and the time to peak plasma creatine kinase MB. Among the patients with transmural electrocardiographic changes, 23% had early peaking of plasma creatine kinase MB, whereas 38% of those with non-transmural changes had early peaking ($p < 0.0009$).

Discussion

Prospective analyses showed that hyaluronidase had a beneficial effect of borderline statistical significance on ejection fraction when it was given for 10 days to

patients randomised to group B (about a third of all patients in MILIS). Retrospective analyses of patients with early peaking of plasma activity creatine kinase MB (25% of the total population) showed improved survival in those treated with hyaluronidase compared with those treated with placebo, with a reduction in both total mortality and deaths from cardiovascular disease. This effect, as in the prospective analyses, was most apparent in patients enrolled into group B. Improved ventricular function, reflected in a rise in ejection fraction from pretreatment values to 8–10 days on hyaluronidase, was also noted in group B patients with early peaking of plasma creatine kinase MB. Patients in group B who were treated with hyaluronidase who had evidence of "non-transmural" ischaemia on the qualifying electrocardiogram showed significant improvement both in survival and ejection fraction compared with placebo treated patients.

There were few significant differences between the baseline characteristics of the placebo and hyaluronidase groups with early peaking of plasma creatine kinase MB or non-transmural electrocardiographic changes; so baseline differences do not account for the beneficial effect of hyaluronidase, either in the group as a whole or those in group B. The similar results of the prospective and retrospective analyses and the combination of improved survival and function, together with the consistent observation that benefit was most noticeable in patients enrolled into group B probably imply some common mechanism.

The frequency of early peaking of plasma creatine kinase MB among the whole population was similar in patients who received placebo or hyaluronidase, indicating that hyaluronidase did not induce early peaking of plasma creatine kinase MB. Also in patients showing early peaking of plasma creatine

Table 4 Comparison of the change in ejection fraction on different treatments by patient group and pretreatment electrocardiographic findings

Group	Type	Treatment	No	Ejection fraction			p value
				Pretreatment	10 days	Change	
A and B	Non-transmural	Placebo	38	44.7 (2.5)	48.9 (2.7)	4.3 (1.8)	0.42
		Hyaluronidase	43	45.7 (2.8)	51.7 (2.4)	6.0 (2.1)	
	Transmural	Placebo	225	47.2 (1.0)	47.8 (1.0)	-0.6 (0.7)	0.27
		Hyaluronidase	212	47.0 (1.0)	48.8 (1.0)	1.8 (0.8)	
A	Non-transmural	Placebo	14	52.1 (4.1)	60.6 (4.0)	8.4 (3.2)	0.05 (P)*
		Hyaluronidase	16	52.4 (5.5)	52.3 (5.3)	-0.1 (2.9)	
	Transmural	Placebo	104	47.6 (1.4)	48.9 (1.5)	1.3 (1.1)	0.59
		Hyaluronidase	91	49.7 (1.5)	51.3 (1.6)	1.6 (1.1)	
B	Non-transmural	Placebo	24	40.3 (2.7)	42.2 (2.8)	1.9 (2.1)	0.007 (H)*
		Hyaluronidase	27	41.7 (2.8)	51.4 (2.4)	9.7 (2.7)	
	Transmural	Placebo	121	46.9 (1.5)	46.9 (1.4)	0.0 (1.0)	0.31
		Hyaluronidase	121	45.0 (1.4)	46.9 (1.3)	1.9 (1.1)	

*Indicates the treatment with most improvement in ventricular function: H, hyaluronidase; P, placebo. Values shown are mean (SEM).

kinase MB, hyaluronidase did not affect infarct size, and therefore the beneficial effect of hyaluronidase was not the result of a reduction of infarct size. This is not unexpected, because treatment was started a mean of eight hours after the onset of symptoms. Instead, these findings suggest that the beneficial effect of hyaluronidase was mediated through some repair or healing process in the early recovery phase.

The early peaking of plasma creatine kinase MB with more rapid washout of creatine kinase reflects better perfusion of the area of infarction. In addition, the infarct size index in patients with early peaking of creatine kinase MB was only about two thirds of that in patients with late peaking of creatine kinase MB. This could result from spontaneous reperfusion, better collateral flow to the ischaemic myocardium in the distribution of the occluded artery, or incomplete obstruction at the initiation of infarction. In any event, it is postulated that early peaking of plasma creatine kinase MB and electrocardiographic changes of non-transmural ischaemia reflect interruption of the evolution of infarction by reperfusion.¹⁵ The following evidence supports this postulate. (a) Infarcts were smaller in patients with early peaking of plasma creatine kinase MB; values in this study were 12.6 for early peaking and 18.9 creatine kinase gram equivalents per square metre for late peaking, despite increased washout of creatine kinase that could lead to overestimation of infarct size. Similarly, infarct size in patients with transmural changes averaged 17.5 creatine kinase gram equivalents per square metre compared with only 6.1 in patients with non-transmural infarction. (b) There is a tendency for myocardial damage to be restricted to the subendocardium in such patients.²² (c) The electrocardiogram of patients with early peaking of plasma creatine kinase MB is more likely to show non-Q-wave infarction.^{23,24} (d) The mortality and morbidity with a single event associated with early peaking of plasma creatine kinase MB are usually less than that associated with late peaking of plasma creatine kinase MB.^{25,26} (e) Patients with non-transmural electrocardiographic changes have a greater tendency to be in an unstable condition and to have recurrent infarction,²³ presumably because of reocclusion of a spontaneously reperfused artery. (f) Coronary arteriography after infarction shows that most patients with non-transmural electrocardiographic changes have incomplete coronary occlusion, while the reverse is true of patients with "transmural" changes.^{27,28} (g) Necropsy data show that contracture necrosis and haemorrhage are more common in non-Q-wave infarction than Q wave infarction,²⁹ suggesting that reperfusion is more common in the former group.

It is possible that the beneficial effects of hyaluron-

idase in patients with early peaking of creatine kinase MB and non-transmural electrocardiographic changes are related to the concomitant improved perfusion of the ischaemic and necrotic myocardium, which would provide a greater access for hyaluronidase to the injured myocardium and permit it to exert its beneficial effect. One hypothesis is that hyaluronidase accelerates recovery of function in surviving but "stunned"³⁰ myocardium, which would account for the improved ventricular function. Experimental studies have shown that hyaluronidase reduces swelling of ischaemic myocytes and increases perfusion of ischaemic myocardium,³¹⁻³⁴ an effect that might attenuate the "no reflow" phenomenon.^{35,36} The hypothesis that the drug exerts its effect only with improved perfusion is consistent with the observation that we saw no beneficial effect in patients with late peaking of plasma activity of creatine kinase MB who presumably do not undergo spontaneous reperfusion.

Hyaluronidase has been shown to cause a short term increase in collateral blood flow³¹ and a degradation product of hyaluronidase has been shown to stimulate the growth of new blood vessels.^{36,37} It is possible that these effects, individually or in combination, could improve ventricular function and survival. Several studies have shown that patients with non-Q-wave infarction are likely to have early peaking of plasma creatine kinase MB and less extensive myocardial damage,^{25,26} but because of subsequent recurrent myocardial infarction they experience a mortality after one year similar to that of patients with Q wave infarction.²⁶ It is possible that hyaluronidase, by stimulating growth of new vessels and collateral flow, could protect against such episodes or attenuate the extent of subsequent injury and thereby improve survival. The explanation for the selective effect of hyaluronidase on patients with early peaking of creatine kinase MB and non-transmural electrocardiographic changes or both may be that delivery of the drug to the jeopardised myocardium is enhanced in these patients.

The second major feature in patients who benefited from hyaluronidase is the consistency with which ventricular function and survival were improved in patients enrolled into group B. Group B patients were identified prospectively in MILIS on the basis of contraindications to propranolol, which included clinical evidence of heart failure, hypotension, and bradycardia. Group A in MILIS was a relatively low risk group; only 19% had suffered a previous myocardial infarction. The left ventricular ejection fraction at the time of admission was well maintained (mean 49%), and in placebo treated patients in group A the ejection fraction remained at an average of 50% 8-10 days after admission. The in-

hospital mortality rate for placebo treated patients in group A was 4%, and the total one year and four year mortality rates were 12% and 15%, respectively. Even if hyaluronidase had a moderately beneficial effect, it could be detected only with a much larger sample of such patients. On the other hand, in group B the left ventricular ejection fraction was significantly lower at entry (mean 44%). In the placebo treated patients in group B, the ejection fraction at hospital discharge was 46%, and the in-hospital, one year, and four year mortality rates (12%, 25%, and 37%, respectively) were significantly higher than in group A. Thus in group B the extent of depression of left ventricular function and the mortality rate in the placebo treated group were such that even if only moderate improvement was produced by the drug it would be detected.

In conclusion, these retrospective findings provide supportive evidence for the beneficial effect of hyaluronidase that was suspected from the analyses carried out on prospectively identified subgroups. The beneficial effect was manifest by both improved ventricular function and survival and occurred in patients in group B. The principal features of the patient population that benefited from hyaluronidase were early peaking of plasma creatine kinase MB and non-transmural changes on the entry electrocardiogram. It may be that in the presence of acute infarction and reperfusion or residual blood flow, hyaluronidase exerts a beneficial effect, resulting in improved left ventricular function. In view of the widespread current use of thrombolytic treatment in patients with acute myocardial infarction, these findings may have important implications for the potential benefits when hyaluronidase is used in combination with reperfusion.

Because the data in this paper are derived from a retrospective subgroup analysis the strength of the conclusions is limited. Therefore, the hypothesis that hyaluronidase has a beneficial effect in these subgroups requires confirmation in prospective studies. In view of the internal consistency of the findings in this study, however, and the increasing importance of reperfusion treatment in acute myocardial infarction, which creates a patient group that is perhaps not unlike the retrospectively identified subgroup which benefited from hyaluronidase in MILIS, such studies deserve serious consideration.

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